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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,006	09/14/2005	Patrick Irving Eacho	X-13055	1872
25885 7590 04/06/2007 ELI LILLY & COMPANY PATENT DIVISION P.O. BOX 6288 INDIANAPOLIS, IN 46206-6288			EXAMINER STOCKTON, LAURA LYNNE	
			ART UNIT	PAPER NUMBER
			1626	
SHORTENED STATUTORY PERIOD OF RESPONSE		NOTIFICATION DATE	DELIVERY MODE	
3 MONTHS		04/06/2007	ELECTRONIC	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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patents@lilly.com

<b>Office Action Summary</b>	Application No. 10/550,006	Applicant(s) EACHO ET AL.	
	Examiner Laura L. Stockton, Ph.D.	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on September 14, 2005 {Prelim. Amendment}.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1, 3-12, 16 and 17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3-12, 16 and 17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/14/2005</u> . | 6) <input type="checkbox"/> Other: _____  |

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## **DETAILED ACTION**

Claims 1, 3-12, 16 and 17 are pending in the application.

### ***Information Disclosure Statement***

The Examiner has considered the Information Disclosure Statement filed on September 14, 2005.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 10-12, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

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one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support was found in the specification or the originally filed claims for the amendments, per the Preliminary Amendment filed September 14, 2005, for:

- a) the change in carbon ranges for the substituent "(C<sub>5</sub>-C<sub>7</sub>)alkyl", under the definition of R<sub>1</sub> in claims 1 and 3;
- b) the added substituent "(C<sub>3</sub>-C<sub>4</sub>)alkylaryl" under the definition of R<sub>1</sub> in claim 1; and
- c) the number of substitutions on the aryl or heterocyclic rings, under the definition of R<sub>1</sub> in claim 1.

Applicant did not state where {page number(s) and line number(s)} support could be found for this changes nor did Applicant make the statement that no new matter has been added. Applicants should specifically point out the support for any amendments. See M.P.E.P. §§

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714.02 and 2163.06. Therefore, the claims lack written description as such.

Claims 10-12, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,

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5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

***The nature of the invention***

Applicant is claiming a methods of inhibiting hepatic lipase and/or endothelial lipase activity, treatment or amelioration of diseases or the effects of elevated hepatic lipase and/or endothelial lipase activity comprising a compound of formula (I). From the reading of the specification, it appears that Applicant is asserting that the instant claimed compounds would be useful for the treatment or prevention of diseases such as hypercholesterolemia, hyperlipidemia, stroke, hypertriglyceridemia, atherosclerosis and related diseases..

***The state of the prior art and the predictability or lack thereof in the art***

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The state of the art is that the prevention of diabetes remains highly unpredictable. Colagiuri et al. {American Journal of Public Health, September 2006, Vol. 96, No. 9, pages 1562-1569} state "Type 2 diabetes is a complex metabolic disorder triggered by lifestyle factors superimposed on a genetic predisposition." Colagiuri et al. also state "Although we recognize the benefits of science, surgery, and service delivery in relation to certain aspects of chronic disease prevention, it is clear that, either independently or in concert, none can achieve the broad scale changes required to prevent diabetes and obesity on a population basis."

According to Bruno et al. {Expert Opinion Emerging Drugs, (2005), 10(4), pages 747-771}, diabetes mellitus is a major health problem that affects over 170 million people worldwide. Park {Diabetes Research and Clinical Practice 66S (2004), S33-S35} states current methods of treating diabetes is inadequate and that current

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strategies to prevent type 2 diabetes mellitus are based on efforts to reduce insulin resistance and to preserve or increase pancreatic beta cell function in high risk individuals. Park also states, "It appears that multiple genes with weak effect are involved in the development of type 2 diabetes mellitus which makes searching diabetogenic genes more complicated."

Further, Choi et al. {Journal of Lipid Research, Volume 43, 2002, pages 1763-1769} indicate that there is some suggestion that endothelial lipase plays a role in the development of atherosclerosis. Choi et al. also state, "However, there is only limited amount of information available about this enzyme" and that more studies are needed. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

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***The amount of direction or guidance present and the presence or absence of working examples***

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the diseases claimed in the pharmaceutical composition and methods. That a single class of compounds can be used to treat, prevent, ameliorate or inhibit all of the diseases embraced by the claims is an incredible finding for which Applicant has not provided persuasive supporting evidence.

***The breadth of the claims***

The breadth of the claims is treating, preventing, ameliorating or inhibiting all diseases which are mediated by hepatic lipase and/or endothelial lipase.

***The quantity of experimentation needed***

The nature of the pharmaceutical arts is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological

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activities for each of the diseases instantly claimed in the composition. The quantity of experimentation needed would be undue when faced with the lack of testing, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and predictability, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

***The level of the skill in the art***

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art, one skilled in the art could not use the claimed invention without undue experimentation.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-6, 9-12, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the additional comma after "(C<sub>5</sub>-C<sub>7</sub>)alkyl" under the definition of R<sub>1</sub> makes it appear that something is missing.

In claim 1, under the definition of R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub>, on the possible substitutions on the alkyl, alkenyl, phenyl or aryl groups, an "and" is needed before "(C<sub>1</sub>-C<sub>6</sub>)haloalkyl".

Claim 3 lacks antecedent basis from claim 1 for R<sub>1</sub> representing:

- a) -O-(C<sub>1</sub>-C<sub>3</sub> alkyl); and
- b) -CF<sub>3</sub>.

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Claim 4 lacks antecedent basis from claim 1 for  $R_1$  representing "benzyl".

Claim 5 lacks antecedent basis from claim 1 for  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  representing:

- a)  $(C_1-C_4)$  alkyl;
- b)  $-O-(C_1-C_3)$  alkyl;
- c)  $(C_5-C_{12})$  cycloalkyl;
- d)  $COOH$ ; and
- e) halo.

Claim 6 lacks antecedent basis from claim 1 for  $R_5$  representing:

- a)  $COOH$ ;
- b) chloro; and
- c) bromo.

Claim 7 is confusing and should be rewritten. A suggestion for re-writing claim 7 is by deleting "of formula(I)..... wherein  $R_1$  through  $R_6$  are selected to provide a compound".

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Claims must, under modern claim practice, stand alone to define an invention, and incorporation into claims by express reference to the specification is not permitted. Ex parte Fressola, 27 USPQ 2d 1608 (1993). It is improper for claims to refer to subject matter not contained therein, even if the subject matter is contained in the specification. Therefore, independent claim 9 is indefinite because the claim fails to identify the structure of formula I in the claim.

In claim 10, the purpose for "inhibiting hepatic lipase and/or endothelial lipase activity" has not been stated in the claim {e.g., to treat what?}.

Claim 10 lacks antecedent basis from claim 1 because of the term "prodrug".

In claim 12, one cannot treat and/or ameliorate at the same time. Only one or the other is possible.

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. {U.S. Pat. 3,517,022} and Takahashi et al. {JP 48-029134}, each taken alone or in combination with each other.

***Determination of the scope and content of the prior art (MPEP***

***§2141.01)***

Applicant claims benzisothiazolone compounds. Miller et al. (columns 1-2; column 8, lines 31-34; and especially the compound in column 2, line 43 and the compound in column 5, lines 66-67) and Takahashi et al. (page 1; and especially the second compound listed on

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page 2) each teach benzisothiazolone compounds that are structurally similar to the instant claimed compounds.

***Ascertainment of the difference between the prior art and the claims***

***(MPEP §2141.02)***

The difference between the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds are generically described in the prior art.

***Finding of prima facie obviousness--rational and motivation (MPEP***

***§2142-2413)***

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., fungicidal).

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of

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obtaining additional beneficial products which would be useful in treating, for example, fungicides. Since Miller et al. and Takahashi et al. teach fungicidal benzisothiazolone compounds that are structurally the same as, or similar to, each other, the combination of the prior art references would also teach the instant claimed invention. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for

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unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

A handwritten signature in cursive script, appearing to read "Laura L. Stockton", written over a horizontal line.

Laura L. Stockton, Ph.D.

Patent Examiner

Art Unit 1626, Group 1620

Technology Center 1600

March 29, 2007